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<p>(54) Title: VALACICLOVIR TABLETS CONTAINING COLLOIDAL SILICON DIOXIDE</p> <p>(57) Abstract</p> <p>A tablet comprising of at least 50 % w/w valaciclovir, and 0.05 to 3 % w/w colloidal silicon dioxide is provided which has excellent hardness and friability properties while still maintaining good lubrication of the tablet granules.</p>				

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## VALACICLOVIR TABLETS CONTAINING COLLOIDAL SILICON DIOXIDE

5 This invention relates to a tablet of the antiviral drug valaciclovir.

The compound 9-[(2-hydroxyethoxy)methyl]guanine, otherwise known as acyclovir possesses potent antiviral activity and is  
10 widely used in the treatment and prophylaxis of viral infections in humans, particularly infections caused by the herpes group of viruses (see, for example, Schaeffer et al, Nature, 272, 583-585 (1978), UK Patent No. 1523865, US Patent No. 4,199,574). However, acyclovir is poorly absorbed from  
15 the gastrointestinal tract upon oral administration and this low bioavailability means that multiple high doses of oral drug may need to be administered, especially for the treatment of less sensitive viruses or infections in order to achieve and maintain effective anti-viral levels in the plasma.

20

The L-valine ester of acyclovir (2-[2-amino-1,6-dihydro-6-oxo-purin-9yl)methoxy]ethyl L-valinate (herein referred to as valaciclovir) has been shown to possess much improved bioavailability whilst retaining the anti-viral properties of  
25 acyclovir. A preferred form of this compound is its hydrochloride salt which is herein referred to as valaciclovir hydrochloride. Valaciclovir and its salts including the hydrochloride salt are disclosed in US Patent No. 4,957,924 (see particular example 1B), European Patent No. 0308065 (see  
30 particularly example IB) and Beauchamp et al, Antiviral Chemistry and Chemotherapy, 3(3), 157-164 (1992) (see particularly page 162 column 1). Tablets of valaciclovir are also generally disclosed in the US Patent No. 4,957,924 and European Patent No. 0308065.

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During development of a tablet formulation containing a high proportion of valaciclovir, we often encountered difficulties in obtaining tablets of sufficient hardness and friability for pharmaceutical handling and for film coating.

5

If the tablet is too friable, it will chip or break during packaging and transport. The US Pharmacopoeia (USP) no. 23, 1995, p1981 at monograph 1216 requires that pharmaceutical tablets have a friability not exceeding 1%. If the tablet is 10 too soft, it will crumble during, tumbling in the film coating pan.

In the reference manual 'Problem Solver' (compiled by FMC Corporation) at pages 8 and 9, the remedies for low tablet 15 hardness are given *inter alia* as increasing the compression force applied to form the tablet, or decreasing the proportion of lubricant in the tablet formulation.

We tried to increase the hardness and friability of 20 valaciclovir tablets by increasing the compression force, by decreasing the proportion of lubricant and increasing the proportion of binder, but found in each case that a sufficiently hard and non-friable tablet could not be produced in a practical way.

25

Furthermore, cracks were found in some tablets as a result of increasing the compression force. Additionally, valaciclovir has 'adhesive' properties in that it can stick to tablet dies and therefore needs to be efficiently lubricated. It is 30 difficult therefore to reduce the proportion of lubricant without causing the tablets to stick. Furthermore, the disintegration time of the valaciclovir tablet is also quite long and therefore any possible solution to the hardness and friability problem could not have a substantial deleterious 35 effect on either the disintegration time or lubrication (as measured by the ejection force) of the tablet formulation.

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It is therefore an object of the invention to provide a robust tablet formulation of valaciclovir and salts thereof which is capable of being film coated and consistently providing tablets having a friability not exceeding 1%, a hardness of  
5 at least 9kP and an ejection force not exceeding 1000 Newtons (1 kN).

The hardness of the tablet should be such that it not only has an acceptable crushing force (as measured by the kP value),  
10 but also that the tablet does not break during tumbling.

It is a further preferred object of the invention to provide a robust formulation which is capable of consistently providing tablets substantially free of cracks.

15 We have now found an effective method of overcoming both of the above friability and hardness problems which involves the use of colloidal silicon dioxide in the tablet formulation.

20 The Handbook of Pharmaceutical Excipients 1994 at p253-256 does not mention colloidal silicon dioxide as an agent to improve the hardness of tablets. Neither does The Theory and Practice of Industrial Pharmacy (third edition) by Lachman, Lieberman and Kanig, mention colloidal silicon dioxide for such a use.  
25

Accordingly in a first aspect of the invention there is provided a tablet comprising at least about 50% w/w valaciclovir or a salt thereof present within the granules of  
30 the tablet, a filler, a binding agent, a lubricant, and about 0.05% to about 3% w/w colloidal silicon dioxide, the lubricant and colloidal silicon dioxide being present extragranularly, wherein the friability of the tablet does not exceed 1%, the hardness is at least 9kP and the ejection force does not  
35 exceed 1000 Newtons.

A tablet of this formulation containing 0.05% to 3% w/w silicon dioxide colloidal is robust, and has a substantially improved friability and hardness. Furthermore such improved properties is achieved while still retaining a satisfactory  
5 disintegration time and lubrication properties, even when the formulation is blended under high shear. An excellent tablet providing acyclovir in a highly bioavailable form is thus provided by virtue of the invention.

10 Preferably the disintegration time of the tablet is not more than about 30 minutes, more preferably not more than about 25 minutes, and most preferably not more than about 20 minutes.

15 The ejection force should not be more than about 1000N, preferably not more than about 800N, more preferably still not more than about 500N for tablets compressed at about 10 to 30 kN, preferably 10 to 20 kN.

20 Valaciclovir or a salt thereof are hereinafter referred to generally as the 'active ingredient'.

25 The 1994 U.S. Pharmacopoeia describes colloidal silicon dioxide (in its monograph) as: a submicroscopic fumed silica prepared by the vapour phase hydrolysis of a silica compound.

30 Preferably the colloidal silicon dioxide is present in amounts of about 0.05% to about 1% w/w of the total formulation, more preferably at about 0.1% to about 1% w/w, and most preferably about 0.1% to about 0.5% w/w. We have found Aerosil (trade mark) and Cab-o-sil (trade mark) to be very suitable.

35 The content of drug in the tablet is at least about 50% w/w, preferably about 60% w/w to about 90% w/w, more preferably still about 65% w/w to about 85% w/w and most preferably about 80% w/w. Preferably the (tapped) bulk density of the drug is about 0.1 to 0.9 g/cc, more preferably 0.3 to 0.7 g/cc, more

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preferably still 0.34 to 0.66 g/cc, and most preferably 0.4 to 0.6g/cc. Suitably the drug is valaciclovir hydrochloride, preferably being of an anhydrous crystalline form including substantially a d-spacing pattern (derived from X-ray powder diffraction) as follows:

d spacing pattern (in Angstroms):

10.20 ± 0.08, 8.10 ± 0.06, 7.27 ± 0.06, 6.08 ± 0.05, 5.83 ±  
10 0.03, 5.37 ± 0.02, 5.23 ± 0.02, 4.89 ± 0.02, 4.42 ± 0.02, 4.06  
± 0.02, 3.71 ± 0.02, 3.39 ± 0.02, 3.32 ± 0.02, 2.91 ± 0.02,  
2.77 ± 0.02.

15 Hereinafter by "anhydrous crystalline form" according to the invention, we mean a crystalline form having substantially the same X-ray powder diffraction pattern as shown in figures 1 to 3, or having substantially the same d spacing pattern as defined above.

20 Preferably the crystal form purity in any such drug lot of anhydrous crystalline valaciclovir hydrochloride used for valaciclovir tablets is as least 70%, more preferably at least 80%, more preferably still at least 90% and most preferably at least 95% anhydrous crystalline valaciclovir hydrochloride  
25 (as characterised above).

In an alternative method for measuring crystal form purity, since the anhydrous crystalline form of valaciclovir hydrochloride contains substantially no water of hydration, 30 the level of other hydrated forms of valaciclovir hydrochloride in any drug lot used for tablets can be measured by the water of hydration content. Preferably any such drug lot of anhydrous crystalline valaciclovir hydrochloride contains no more than 3% w/w, more preferably no more than 2% w/w, more preferably still not more than 1 % w/w and most 35 preferably not more than 0. 5 % w/w water of hydration.

This water of hydration content is measured by the Karl Fischer method which is well known in the art and is described in the 1990 U.S. Pharmacopoeia at pages 1619-1621, and the European Pharmacopoeia, second edition (1 992), part 2, 5 sixteenth fascicle at v. 3.5.6-1.

Advantageously the filler is a cellulosic filler and is at least partly present extragranularly, which mitigates stress cracking of the tablet. A tablet formulation of the invention 10 including colloidal silicon dioxide and extragranular cellulosic filler (such as microcrystalline cellulose) appears to have a synergistic effect and is particularly good and robust in that tablets of valaciclovir can consistently be made to an acceptable hardness without introducing stress 15 cracks even under a high compression force.

According to a preferred aspect of the invention there is provided a tablet comprising at least 50% w/w valaciclovir or a salt thereof, a binding agent, a lubricant, 0.05 to 3% w/w 20 colloidal silicon dioxide, and 3 to 30% of a cellulosic filler; wherein the valaciclovir or salt thereof is present within the granules of the tablet, the lubricant, colloidal silicon dioxide, and at least a portion of the cellulosic filler is present extragranularly; wherein the friability of 25 the tablet does not exceed 1%, the hardness is at least 9kP, and the ejection force does not exceed 1000N.

Preferably the cellulosic filler is microcrystalline cellulose (e.g. Avicel); and is preferably present at 5 to 15% w/w, most preferably about 10% w/w. The particle size of the cellulosic filler is preferably 20 to 300 $\mu$ , more preferably 30 to 200 $\mu$ , and most preferably 50 to 100 $\mu$ .

According to a further aspect of the invention there is 35 provided a tablet comprising at least 50% w/w valaciclovir or a salt thereof, a binding agent, a lubricant, and about 3% to

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30% w/w of a cellulostic filler, the valaciclovir or its salt being present within the granules of the tablet and the lubricant and cellulostic filler being present extragranularly.

5

The binding agent serves, for example, to bind the primary and secondary particles together and improve tablet hardness. Preferably the binding agent is present in an amount of about 1% to about 5% w/w, more preferably at about 2% to about 4% w/w, and is suitably a non-starch based binder such as methylcellulose or most preferably povidone. The grade of povidone is advantageously K30 and most preferably K90.

10 The binding agent such as the povidone, can be dissolved in the granulating solvent (such as water) before adding to the drug, but preferably it is added (at least partly) dry to the drug and other excipients and then the granulating solution (such as povidone in water) added.

15 20 The lubricant is suitably present in an amount of about 0.1% to about 2.0% w/w, preferably about 0.1% to about 1.0% w/w. Although lubricants such as talc or sodium lauryl sulphate are suitable, preferably the lubricant is a stearate derivative, more preferably an alkali metal stearate, such as magnesium stearate. The above amounts apply to the stearate, and they are ideally present in amount of at about 0.3% to about 0.6% w/w.

25 30 Although valaciclovir is very soluble, especially in its salt form, it is preferable if a disintegrating agent is present in the tablet formulation, suitably in an amount of about 0.5 to about 20% w/w, more preferably at about 0.5% to 7.0% w/w. The disintegrating agent is advantageously present within the granules of the tablet and can be added before or after the binding, agent. Clays such as kaolin, bentonite or veegum (trademark), and celluloses such as microcrystalline cellulose

or croscarmellose sodium e.g. Ac-Di-Sol (trademark) maybe used as disintegrants. Preferably a non-ionic disintegrant such as crospovidone is used. Preferably, the crospovidone is present at about 0.5% to about 7.0% w/w, more preferably about 5 2 to about 5% w/w, and preferably a portion is present intragranularly.

A further aspect of the invention provides a process for preparing a tablet comprising at least about 50% w/w 10 valaciclovir or a salt thereof, a binding agent, a filler, a lubricant, and about 0.05 to 3.0% w/w colloidal silicon dioxide; wherein the hardness of the tablet is at least 9 kp, the friability is not more than 1%, and the ejection force is not more than 1000N; said process comprising forming granules 15 which include valaciclovir or a salt thereof and then blending the lubricant and colloidal silicon dioxide with said granules.

Preferably said process comprises forming granules by mixing 20 said valaciclovir or salt, optionally a binding agent or a portion thereof, and optionally the filler or a portion thereof; granulating with a granulating solution to form granules or dissolving the binding agent or a portion in the granulating solution before adding to valaciclovir; drying the 25 granules; blending the granules with the lubricant, colloidal silicon dioxide, and optional filler or a portion thereof; and then compressing the blended mixture to form a tablet.

A preferred aspect of the invention provides a process for 30 preparing a tablet comprising at least 50% w/w valaciclovir or a salt thereof, a binding agent, a lubricant, 0.05 to 3% w/w colloidal silicon dioxide, and 3 to 30% w/w of a cellulostic filler; wherein the hardness of the tablet is at least 9kP, the friability is not more than 1%, and the ejection force is not more than 1000N; said process comprising 35 forming granules by mixing the valaciclovir or salt, optional

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binding agent or a portion thereof, and optionally a portion of cellulostic filler; granulating with a granulating solution to form granules or dissolving the binding agent or a portion thereof in the granulating solution before adding to  
5 valaciclovir; drying the granules; blending the granules with the lubricant, colloidal silicon dioxide, and at least a portion of the cellulostic filler; and then compressing the blended mixture to form a tablet.

10 The colloidal silicon dioxide can be first blended with the lubricant, preferably a stearate derivative (e.g. magnesium stearate) before blending with the granules or it can be added separately from the lubricant. When the lubricant is a stearate derivative, preferably the ratio of stearate to  
15 colloidal silicon dioxide is about 1:1 to 10:1, more preferable about 1: I to about 3: 1.

The present invention also provides a tablet (as described above) for use in medical therapy, e.g. in the treatment of  
20 a viral disease in an animal, e.g. a mammal such as a human. The compound is especially useful for the treatment of diseases caused by various DNA viruses , such as herpes infections, for example, herpes simplex 1 and 2, varicella zoster, cytomegalovirus, Epstein-Barr viruses or human herpes  
25 virus-6 (HHV-6) as well as diseases caused by hepatitis B. The active compound can also be used for the treatment of papilloma or wart virus infections and, may furthermore be administered in combination with other therapeutic agents, for example with zidovudine, to treat retroviral associated  
30 infections in particular HIV infections.

In addition to its use in human medical therapy, the active compound can be administered to other animals for treatment of viral diseases, e.g. to other mammals.

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The present tablet also provides a method for the treatment of a viral infection, particularly a herpes viral infection, in an animal, e.g. a mammal such as a human, which comprises administering to the host one or more tablets of the invention  
5 to provide an effective antiviral amount of the active compound.

The present invention also provides the use of the active compound in the preparation of a tablet of the invention for  
10 the treatment of a viral infection.

A tablet of the invention may be administered by any route appropriate to the condition to be treated, but the preferred route of administration is oral. Although tablets generally  
15 are included within the scope of the invention, for example a dispersible tablet or chewable tablet, preferably the tablet is a swallowable tablet, most preferably a film-coated swallowable tablet. It will be appreciated however, that the preferred route may vary with, for example, the condition of  
20 the recipient.

For each of the above-indicated utilities and indications the amounts required of the active ingredient (as above defined) will depend upon a number of factors including the severity  
25 of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician or veterinarian. In general however, for each of these utilities and indications, a suitable effective dose will be in the range 1 to 150 mg per kilogram bodyweight  
30 of recipient per day, preferably in the range 5 to 120 mg per kilogram bodyweight per day (Unless otherwise indicated, all weights of the active ingredient are calculated with respect to the free base valaciclovir). The desired dose is preferably presented as one, two, three or four or more sub-doses administered at appropriate intervals throughout the  
35 day. These sub-doses may be administered in unit dosage

forms, for example, containing about 50 to 2000 mg, preferably about 250, 500, 1000 or 2000mg of active ingredient per unit dose form.

5    The following dosage regimes are given for guidance:  
treatment of herpes simplex virus types 1 and 2 infection:-  
total daily dose of about 1 or 2g administered at 500mg twice  
a day or 1g twice a day for 5 to 10 days; suppression of  
herpes simplex virus types 1 and 2 infections:- total daily  
10   dose about 250mg to 1g for about one to ten years (depending  
on the patient);  
treatment of varicella zoster virus infections (for example  
shingles):- daily dose about 3g administered at 1g three  
times a day for seven days; suppression of cytomegalovirus  
15   infections:- total daily dose about 8g administered at 2g 4  
times a day. For transplant patients this daily dose is  
administered for three to six months for the period at  
risk; and for HIV positive patients said daily dose is  
administered as usually indicated for improving quality of  
20   life, for example for two years or more.

Early results now indicate that valaciclovir can be used in  
the effective suppression of recurrent genital herpes at a  
once daily dose of from about 200 mg to about 1000 mg for  
25   an effective treatment period. The most likely daily  
dosages are 250 mg, 500 mg or 1000 mg.

Valaciclovir hydrochloride was made as described below:

Example 1

30   A. 2-[2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl]  
methoxylethyl-N-[(benzoloxoxy)carbonyl]-L-valinate  
CBZ-L-valine (170 g) was dissolved in dimethylformamide  
(DMF) (750 ml) and cooled. A cold solution of N,N-dicyclo-  
hexyl-carbodiimide (DCC) (156.7 g) in DMF (266 ml) was  
35   added and stirred with cooling. Acyclovir (10.1 g) was  
added in a single portion, and then 4-(dimethylamino)  
pyridine (9.4 g) was added while maintaining cooling. The  
mixture was stirred cold overnight. A white

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precipitate of the by-product was then removed by filtration. The filtrate was reduced in volume by vacuum distillation and the concentrate treated with water (663 ml) then heated to 70°C. The suspension was cooled to 5 20°C, filtered and the solid washed with water.

The damp, crude material was then purified by recrystallisation from denatured alcohol (1.2 litres) to afford the title compound as a damp white crystalline solid 10 (281.5 g).

B. 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl-L-valinate hydrochloride

15 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl-N-[(benzyloxy)carbonyl]-L-valinate (175 g) was charged to aqueous denatured alcohol (335 ml/795 ml) and heated to reflux. The solution was then cooled to 40°C. The suspension was treated with 5% palladium on carbon catalyst 20 (35 g wet weight 50% wet with water) then formic acid (30.6 ml of 90% w/w) added over 1 hour. The reaction mixture was stirred for a further 1 hour then a second charge of formic acid made (19.5 ml) and the mixture filtered to remove the catalyst. The filter cake was washed with denatured 25 alcohol and the combined filtrates were treated with concentrated hydrochloric acid (33.7 ml) and the resultant mixture was concentrated by vacuum distillation.

Acetone (1295 ml) was then added over 15 minutes and the 30 suspension stirred for 1 hour before filtering off the product. The solid was then slurried with acetone (circa. 530 ml), refiltered and dried at 60°C in vacuo to give the title compound (1123 g : 81.6%).

35 A 15 g sample of this material was combined with denatured alcohol (circa. 7 ml), to moisten and was heated with

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agitation at 60°C overnight in a closed flask to avoid loss of alcohol and maintain the dampness of the mixture. The mixture was then dried at 60°C in vacuo to afford the product as the desired morphic form.

5

Physical Data:

Karl Fischer value : 0.9% w/w water.

10 The X-ray powder diffraction patterns of the product of example 1B are shown in Figure 1 of the accompanying drawings.

The d spacings and further X-ray diffraction data are shown in Table 1.

15

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Table 1

5	Peak No:	Angle I/I <sub>max</sub> (%)	Peak (degrees)	Peak (counts)	d Spacing pattern	Error in d (± Å) (Å)
10	1	3.56	680	24.8	0.5	24
	2	8.62	1151	10.25	0.08	39
	3	9.42	87	9.38	0.07	3
	4	10.86	1438	8.14	0.06	49
	5	12.10	835	7.31	0.06	28
	6	13.22	198	6.69	0.05	6
15	7	14.49	2172	6.11	0.05	75
	8	15.12	455	5.85	0.03	15
	9	15.90	352	5.57	0.02	12
	10	16.45	1969	5.38	0.02	68
	11	16.90	744	5.24	0.02	25
	12	17.33	119	5.11	0.02	4
20	13	18.12	1013	4.89	0.02	35
	14	22.71	1429	4.43	0.02	49
	15	20.55	256	4.32	0.02	8
	16	21.21	370	4.19	0.02	12
	17	21.83	753	4.07	0.02	26
	18	22.71	95	3.91	0.02	3
25	19	23.95	2893	3.71	0.02	100
	20	25.10	171	3.54	0.02	5
	21	26.21	1784	3.40	0.02	61
	22	26.89	428	3.31	0.02	14
	23	27.08	373	3.29	0.02	12
	24	28.02	158	3.18	0.02	5
30	25	28.27	161	3.15	0.02	5
	26	28.91	391	3.09	0.02	13
	27	29.68	191	3.01	0.02	6
	28	30.55	502	2.92	0.02	17
	29	31.34	110	2.85	0.02	3
	30	31.58	98	2.83	0.02	3
35	31	32.13	597	2.78	0.02	20
	32	32.96	260	2.72	0.02	8
	33	33.99	344	2.64	0.02	11
	34	34.38	374	2.61	0.02	12
	35	35.12	141	2.55	0.02	4
	36	36.78	408	2.44	0.02	14
45	37	38.71	101	2.32	0.02	3

I/I<sub>max</sub> = (peak height/max. peak ht) x 100

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The powder sample used to produce the above X-ray diffraction data was prepared by an equivalent method as the powder sample used to produce the X-ray diffraction date of table 2 (described hereinafter) except that for the 5 above data the following preparation was used to prepare the powder sample.

The sample was prepared by milling 1 g of sample in a plastic cup using two acrylic balls for 5 minutes with a 10 Chemplex Spectromill. The samples were then back packed against a glass slide to a depth of 2 mm.

The X-ray diffraction scan was obtained using a Scintag PADV diffractometer in the step scan mode at 0.02° per step 15 and a 10 second count per step. The sample holder was spun at 1 rotation per second during the scan. Additional setting as described below.

X-ray generator: 45 kV, 40 mA  
20 Radiation: Copper K alpha radiation  
Fixed divergent slit: 1 mm  
Incident scatter slit: 2 mm  
Diffracted scatter slit: 0.5 mm  
Receiving slit: 0.3 mm  
25 Goniometer radius: 235 mm  
Detector: Scintillation with a graphite monochromator.

The peak intensities are reported as absolute counts of the peak top. The intensity units on the X-ray diffraction 30 plot are counts/sec. The absolute counts = counts/sec x count time = counts/sec x 10 sec. The peak intensities in the table have been corrected for background and copper K alpha II X-ray wavelength contribution.

Example 2

A. 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxylethyl-N-[(benzyloxy)carbonyl]-L-valinate

5

CBZ-L-valine (167 g) was dissolved in dimethylformamide (DMF) (750 ml) and cooled to 0.5°C. A cold solution of N,N-dicyclohexylcarbodiimide (DCC) (153.5 g) in DMF (266 ml) was added followed by acyclovir (111.7 g) in a single portion. 4(Dimethylamino)pyridine (9.4 g) was then added and the mixture stirred cold overnight. A white precipitate of the by-product was then removed by filtration. The solvent was partially removed by vacuum distillation and the concentrate treated with water (663 ml) then heated to 70°C. The suspension was cooled to 20°C, filtered and the solid washed with water.

10 The damp, crude material was then purified by recrystallisation from denatured alcohol (1.2 litres) to afford the title compound as a damp white crystalline solid (215.3 g).

B. 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxylethyl-L-valinate hydrochloride

20

25 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxylethyl-N-[(benzyloxy)carbonyl]-L-valinate (200 g) was charged to aqueous denatured alcohol (382 ml / 908 ml) and heated to reflux to dissolve solids. The solution was cooled to 40°C. The suspension was treated with a 50% w/w paste of 30 5% palladium on carbon catalyst and water (40 g) then formic acid (96% w/w : 32.8 ml) added over 1 hour. The reaction mixture was stirred for a further 1 hour then a second charge of formic acid made (20.88 ml) and the 35 mixture filtered to remove the catalyst. The filtrate was

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treated with concentrated hydrochloric acid (38.56 ml) and the resultant mixture was concentrated under vacuum.

5 Acetone (1480 ml) was then added over 15 minutes and the suspension stirred for 1 hour before filtering off the product. The solid was then slurried with acetone (ca. 500 ml), refiltered and dried at 60°C *in vacuo* to give the title compound (137.75 g : 87.6%).

10 A 10 g sample of this material was combined with denatured alcohol (3.5 ml), heated at 60°C for several hours and the solvent then removed *in vacuo* to afford the product as the desired morphic form.

15 Crystal Form Purity: the sample of example 2(B) contained above 90% of the anhydrous crystalline form valaciclovir.

20 The X-ray powder diffraction patterns of the product of example 2(B) are shown in Figures 2 and 3 of the accompanying drawings in which:-

Fig 2 is a linear plot X-ray diffractogram; and

Fig 3 is a square root plot X-ray diffractogram.

25 The d spacings and further X-ray diffraction data are shown in Table 2

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Table 2

Peak No:	Angle (degrees)	Peak (counts)	d Spacing pattern (Å)	I/I <sub>max</sub> (%)
5	1	3.62	2673	24.40
	2	7.21	119	12.26
	3	8.64	1910	10.22
10	4	9.43	180	9.37
	5	10.86	2652	8.14
	6	12.12	734	7.30
	7	13.24	615	6.68
	8	13.77	106	6.42
15	9	14.50	2333	6.11
	10	15.14	635	5.85
	11	15.89	511	5.57
	12	16.44	2652	5.39
	13	16.90	1267	5.24
20	14	17.33	475	5.11
	15	18.13	1648	4.89
	16	20.05	2172	4.43
	17	20.56	640	4.32
	18	21.20	1096	4.19
25	19	21.78	2034	4.08
	20	21.90	1384	4.06
	21	22.66	729	3.92
	22	23.94	7621	3.71
30	23	24.39	1624	3.65
	24	25.11	967	3.54
	25	25.86	2460	3.44
	26	26.21	5127	3.40
	27	26.82	1892	3.32
	28	26.89	1927	3.31
35	29	27.19	1429	3.28
	30	27.99	1156	3.18
	31	28.35	1076	3.15
	32	28.87	1722	3.09
	33	28.94	1529	3.08
40	34	29.62	1274	3.01
	35	30.56	1673	2.92
	36	31.30	999	2.86
	37	32.25	2570	2.77
	38	33.04	1376	2.71
45	39	34.00	1806	2.63
	40	34.45	1225	2.60
	41	35.13	1149	2.55
	42	36.77	1600	2.44
	43	38.01	576	2.37
50	44	38.76	729	2.32
	45	39.52	524	2.28
	46	40.70	751	2.22

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Table 2 Continued

	Peak No:	Angle (degrees)	Peak (counts)	d Spacing pattern (Å)	I/I <sub>max</sub> (%)
5	47	41.28	870	2.19	11
	48	41.88	686	2.16	9
	49	42.47	718	2.13	9
	10 50	43.40	548	2.08	7
	51	44.53	729	2.03	10

The diffraction patterns of the product of example 2B were generated on a Phillips PW1800 Automatic X-ray Powder Diffractometer using a scan of 2 to 45 2θ with step intervals of 0.02 degrees and an integration time of 4 seconds per step.

Generator settings: 40 KV, 45 mA, Cu alpha 1,2 wavelengths: 1.54060, 1.54439 Å; Step size, sample time: 0.020 deg, 4.00 s, 0,005 deg/s; monochromator used: yes; divergence slit: automatic (irradiated sample length: 10.0 mm); peak angle range: 2.000 - 45.000 deg; range in D spacing: 44.1372 - 2.01289 Å; peak position criterion: top of smoothed data; cryst peak width range: 0.00 - 2.00 deg; minimum peak significance: 0.75 maximum intensity: 7621 cts, 1905.3 cps.

The powder sample was prepared as follows:

30 A 1 gram portion of valaciclovir hydrochloride was transferred to a Retsch 10 ml polystyrol container ref 31-762 containing 2 acrylic balls ref 26-253 and was then ground to a very fine powder using a Retsch MM2 miser mill set at 100% power for five minutes. The ground powder was 35 back loaded into a Philips PW1811/10 sample holder which had been placed inverted on a perfectly smooth surface (e.g. that afforded by a glass plate or a highly polished metal sheet). The powder was then packed into the holder and further powder added and packed until the holder was 40 full. A Philips PW 1811 00 bottom plate was then clamped

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into the holder and the entire assembly was then inverted before removing the glass/metal plate in an upwards direction to reveal the smooth sample surface which was flush with that of the holder.

5

The invention is illustrated below in the following examples and the properties of the tablets show in table 3 hereafter.

10

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Example	3	4	5
Ingredients	mg/ tablet	kg/ Batch	w/w
		mg/ Tablet	kg/ Batch
Core (intra granular):			
valaciclovir hydrochloride *2	576.5	0.9916	82.0
microcrystalline cellulose (Avicel PH101)	70.0	0.1204	10.1
crossporidone	28.0	0.04816	4.0
povidone K30			
povidone K90	22.0	0.03784	3.1
extragranular:			
micro crystalline cellulose (Avicel PH101)	-	-	-
crospovidone	-	-	-
colloidal silicon dioxide (CAB-O- SIL M-S®)	2.0	0.00160	0.3
magnesium sterate	4.0	0.0032	0.6
TOTAL WEIGHT	702.5	1.2028	100.0
		696.5	1.198
			100.0
			700.5
			1.2012
			100.0

- 21a -

Example		6		7
Ingredients		mg/ Tablet	kg/ Batch	w/w
Core (intra granular):				
valaciclovir hydrochloride *2	576.5	0.9973	82.3	576.5
microcrystalline cellulose (Avicel PH101)	-	-	-	0.9973
crossporidone	14.0	0.02422	2.0	82.0
povidone K30	22.0	0.03806	3.1	-
povidone K90	22.0	0.03806	22.0	0.02422
extragranular:				2.0
micro crystalline cellulose (Avicel PH101)	70.0	0.05600	10.0	0.03806
crospovidone	14.0	0.11200	2.0	3.1
colloidal silicon dioxide (CAB-O-SIL M-5®)	-	-	-	0.05600
magnesium stearate	4.0	0.00320	0.6	10.0
TOTAL WEIGHT	700.5	1.12998	100.0	702.5
				1.13158
				100.0

- \* Bulk density 0.6g/cc after 50 taps (anhydrous crystalline form); Karl Fischer water content = 0.4.
- 1. Core weight per batch : 0.5572kg for examples 3, 4 and 5; 0.4900kg for examples 6 and 7.
- 2. Factor 1.153 = 100
- 3. Average particle size about 50µ

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Example	8		9	
Ingredients	mg/ tablet	w/w	mg/ tablet	w/w
valaciclovir hydrochloride*	615	65.80	615	65.74
lactose	205	21.93	205	21.91
microcrystalline <sup>1</sup> cellulose (Avicel PH101) (intragranular)	75	8.02	75	8.02
povidone K30	18	19.3	18	1.92
crospovidone (intragranular)	18	1.93	18	1.92
colloidal silicon dioxide (Aerosil 200)	0.0	0.0	0.69	0.10
magnesium stearate	3.6	0.39	3.6	0.38
TOTAL WEIGHT	934.6	100.0	935.5	100

\* bulk density 0.45 g/cc after 50 taps (anhydrous crystalline form)

1 Average particle size about 50μ.

Example	10		11	
Ingredients	mg/ tablet	w/w	mg/ tablet	w/w
valaciclovir hydrochloride*	580	81.01	580	82.60
lactose	-	-	-	-
microcrystalline cellulose <sup>2</sup> (Avicel PH101) (intragranular)	70	9.78	-	-
microcrystalline cellulose (extragranular)	-	-	70.4	10.03
povidone K30	35	4.89	-	-
povidone K90	-	-	21.7	3.09
crospovidone (intragranular)	28	3.91	12	1.71
crospovidone (extragranular)	-	-	14.1	2.01
magnesium stearate	3.0	0.42	4.0	0.57
<b>TOTAL WEIGHT</b>	<b>716</b>	<b>100.0</b>	<b>702.2</b>	<b>100.0</b>

\* bulk density 0.38 g/cc after 50 taps (anhydrous crystalline form)

25 1 Average particle size about 50μ.

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The tablets of the examples were made as disclosed below.

Examples 3 to 7

5      Step 1.    The core ingredients were sifted with a 20 mesh hand screen, and then blended in an appropriately sized V-shell blender for 10 minutes.

10     Step 2.    The blended powders from Step 1 were then granulated in a 10 litre high shear mixer (model-SP1) by adding pure water while mixing. Approximately 11-14% water, w/w of the core ingredients was then added and the mixture massed for 3 to 4½ minutes.

15     Step 3.    The granule from Step 2 was dried in a tray (examples 5, 6 and 7) or vacuum (examples 3 and 4) drier (model-SP1) at a temperature of 50°C to an acceptable moisture content of approximately 20     1.0 to 2.0 % L.O.D.

25     Step 4.    The remaining ingredients were sifted through a 20 mesh screen and added to the core ingredients of step 3, and then the mixture was sifted using a Comil Model 197 AS fitted with a 0.062" screen.

30     Step 5.    The mixture was then blended in an appropriately sized V-shell blender for 5 minutes.

35     Step 6.    The blended granule from Step 5 was compressed on a Manesty Beta Press fitted with capsule shaped tooling, 18.25 mm x 7.14 mm, at a compression weight of approximately 700 mg and a compression force of about 14.5 to 18 kN.

Step 7   The tablets can then optionally be film coated by

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using standard methods such as using white colour concentrate, methylhydroxypropylcellulose, titanium dioxide, polyethylene glycol and polysorbate.

5

Hardness (crushing force through the long axis) was measured using a Key hardness tester, Model HT-300. Friability (percent weight loss after 100, six inch drops) was measured in accordance with the USP no. 23, 1995, p1981 at monograph 1216, using an Erweka friability tester, Model TA-3. Physical properties were measured at comparable compression forces. The disintegration time was measured in accordance with the monograph in USP 23 (1995) at page 1790.

15

Examples 8 and 9

Step 1. The following ingredients as shown were sifted with a hand screen.

20

30 Mesh

valaciclovir hydrochloride	5.289 kg
lactose	1.763 kg
microcrystalline Cellulose	0.6450 kg
povidone K30	0. 1548 kg
crospovidone	0. 1548 kg

25

60 Mesh

magnesium stearate	0.03096 kg
colloidal silicon dioxide (CSD)	0.002598 kg

30

Step 2. The 30 mesh sifted ingredients from Step I were then blended, excluding the povidone, in a 1 cubic foot V-shell blender for 10 minutes.

35

Step 3. 1.540 kg of SD3A alcohol (ethanol denatured with 5% methanol) was then mixed with 0.6600 kg of purified water and the screened povidone, 0.1548

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kg, was dissolved in 0.6192 kg of the mixed solvents by hand stirring.

Step 4. The blended powders from Step 2 were then granulated in a 1 cubic foot Littleford Lodige mixer by adding the dissolved povidone while mixing. 1.315 kg of more mixed solvent was added and the mixture massed for seven minutes total as shown below.

10 Ploughs 7 min Choppers 6.5 min

Step 5. The granule from Step 4 was then dried in a Fluid Bed Dryer (Glatt GPCG5) with an inlet air temperature of 50°C to any acceptable moisture content of approximately 1.0 to 3.0% L.O.D.

15

Step 6. The granule from Step 5 was then sifted using a Fitz Mill Model M fitted with a 30 mesh screen, with knives forward, operating at medium speed.

20

Step 7. The screened magnesium stearate from step 1 was added to the granule from Step 6 and blended for 5 minutes using the blender from Step 2. This was labelled as example 10 (2.650kg).

25

Step 8. Part of the blended granule from Step 7 was compressed on a Manesty Beta Press fitted with oval tooling, 19.1 mm x 10.2 mm, at a compression weight of approximately 934.6 mg.

30

Step 9. The remainder of the lubricated granule 2.650 kg (from Step 7) was weighed and the sifted CSD from step I added, then dispersed by hand and the mixture blended for 5 minutes in the blender from Step 3. This portion was labelled as Example 11. The mixture was compressed to form tablets.

35

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Examples 10 and 11 were manufactured in a substantially similar manner to Examples 9 an 10 with the following exceptions.

- 5      1.      All ingredients were sifted through a 20 mesh sieve.
2.      Drug and intragranular ingredients were blended for 10 minutes.
- 10     3.      The amounts of water and SD3A alcohol were adjusted for the difference in batch size.
4.      Dried granule was milled using a Comil Model 197AS with 0.062" screen.
5.      Example 11 was dried in a tray drier.
6.      The magnesium stearate was blended for 10 minutes after 10 minutes preblend of the milled granule and other ingredients.

**TABLE 3**

Example Numbers	Compression Force (kN)	Hardness (kP)	Friability (%)	Disintegration Time (mins)	Ejection Force (Newtons)	Stress Cracks (after heating <sup>1</sup> )
3a)	15.256	10.0	0.035	15.36	395	Yes
3b)	17.896	13.3	0.041	16.60	452	Yes
4	14.746	8.2 <sup>3</sup>	0.107	13.94	305	Yes <sup>2</sup>
5a)	15.343	9.9	0.15	17.95	300	Yes
5b)	17.956	12.5	0.10	19.96	329	Yes
6a)	15.658	11.9	0.15	18.04	306	Yes/faint
6b)	17.771	14.7	0.14	17.68	324	Yes
7a)	15.495	12.6	0.13	18.89	366	No
7b)	17.896	15.3	0.14	20.11	411	No
8a)	14.3	5.9	1.78	not available (N/A)	410	
8b)	31.4	9.7	1.70	N/A	450	
9a)	14.7	13.6	0.04	10.3	332	
9b)	30.7	22.8	0.03 <sup>3</sup>	12.6	330	
10	Setting 6	14.4		N/A	B/A	Yes
11	Setting 7	15.5		N/A	N/A	No

1. Heated in a 50°C forced air oven to simulate film coating.
2. Stress cracks before and after heating.
3. One tablet broke in half (unacceptable hardness)

As can be seen from the results, the tablet of example 4 (which lacks colloidal silicon dioxide and has microcrystalline cellulose extragranularly) broke in half during tumbling, to simulate film coating conditions. The 5 hardness of the tablet is therefore totally unacceptable. On the contrary, when colloidal silicon dioxide was added (example 3) the tablet surprisingly did not break and furthermore the disintegration time and ejection force increased by substantially less than would be expected.

10

The tablets of examples 5 and 6, like that of example 3, developed stress cracks after heating. In the tablet of example 3 there was present colloidal silicon dioxide and intragranular microcrystalline cellulose; in example 5 the 15 microcrystalline cellulose was also intragranular, but there was no colloidal silicon dioxide; and in example 6 again there was no colloidal silicon dioxide, but the microcrystalline cellulose was extragranular. Surprisingly, however, when colloidal silicon dioxide is 20 present and the microcrystalline cellulose is extragranular, there appears to be synergy which prevents stress cracking. This effect can be seen in the table of example 7 where there are no stress cracks, and furthermore the hardness and friability were good. As with the table 25 of example 3, the disintegration and ejection force were increased substantially less than would be expected.

As can also be seen from comparative example 8a) the hardness value is very low and the friability fails the US 30 Pharmacopoeia (USP) limit of 1%. Even at the very high compression force used in example 8b), the friability still fails the USP test.

In contrast on the addition of about 0.1% w/w of colloidal 35 silicon dioxide (in example 9a and b), hardness and friability have dramatically improved. Furthermore the

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ejection force, which was good before the addition of colloidal silicon dioxide is still good, and in fact actually improved on its addition. The disintegration time of the tablets of example 9 is also very satisfactory.

5

Additionally when the formulation of example 11 is repeated incorporating colloidal silicon dioxide in amounts ranging from 0.05 to 3% w/w, excellent tablets can be consistently produced having a high hardness and low friability value,  
10 substantially free of stress-cracks.

The robust tablet formulation of the invention therefore can consistently provide valaciclovir tablets having excellent handling characteristics which are suitable for  
15 film coating and which still have an adequate lubricating and disintegration time.

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CLAIMS

1. A tablet comprising at least about 50% w/w valaciclovir or a salt thereof, a filler, a binding agent, a lubricant and about 0.05 to about 3% w/w colloidal silicon dioxide wherein the valaciclovir or a salt thereof is present within the granules of the tablet, the lubricant and silicon dioxide being present extragranularly; wherein the friability of the tablet does not exceed 1%, the hardness is at least 8 kP, and the ejection force does not exceed 1000 Newtons.  
5
2. A tablet as claimed in any one of the preceding claims wherein the colloidal silicon dioxide is present in an amount of about 0.1% to about 0.5% w/w.  
15
3. A tablet as claimed in claims 1 or 2 wherein the filler is present in an amount of about 3% w/w to about 30% w/w.  
20
4. A tablet as claimed in claim 3 wherein the filler is and is present at about 5% to about 15% w/w.  
25
5. A tablet as claimed in claim 4 wherein the filler is a cellulostic filler.
6. A tablet as claimed in claims 4 or 5 wherein the cellulostic filler is at least partly present extragranularly.  
30
7. A tablet as claimed in Claims 5 or 6, wherein the particle size of the cellulostic filler is about 20 to about 300 $\mu$ .  
35

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8. A tablet as claimed in any one of the preceding claims wherein the binding agent is present at about 1 % to about 5 % w/w.
- 5 9. A tablet as claimed in any one of the preceding claims wherein the binding agent is methylcellulose or povidone.
10. A tablet as claimed in claim 9 wherein the binding agent is povidone.
11. A tablet as claimed in claim 10 wherein the povidone is povidone K90 grade.
- 15 12. A tablet as claimed in any one of the preceding claims wherein the lubricant is present at about 0. 1% to about 2.0% w/w.
- 20 13. A tablet as claimed in claim 12 wherein the lubricant is a stearate derivative.
14. A tablet as claimed in claim 13 wherein the lubricant is magnesium stearate and is present at about 0. 1% to about 1.0% w/w.
- 25 15. A tablet as claimed in any one of the preceding claims wherein the valaciclovir or its salt is present at about 65% to about 85% w/w.
- 30 16. A tablet as claimed in any one of the preceding claims comprising valaciclovir hydrochloride.
17. A tablet as claimed in claim 16 wherein the valaciclovir hydrochloride is anhydrous crystalline form including substantially a d spacing pattern as follows:

d spacing pattern (in Angstroms):

10.20 ± 0.08, 8.10 ± 0.06, 7.27 ± 0.06, 6.08 ±  
5 0.05, 5.83 ± 0.03, 5.37 ± 0.02, 5.23 ± 0.02, 4.89  
± 0.02, 4.42 ± 0.02, 4.06 ± 0.02, 3.71 ± 0.02, 3.39  
± 0.02, 3.32 ± 0.02, 2.91 ± 0.02, 2.77 ± 0.02.

18. A tablet as claimed in any one of the preceding  
10 claims wherein the tapped bulk density of  
valaciclovir or salt thereof is about 0.1 to about  
0.9g/cc.

19. A tablet as claimed in any one of the preceding  
15 claims which further includes a disintegrating  
agent present at about 0.5% to about 20% w/w.

20. A tablet as claimed in claim 19 wherein the  
disintegrating agent is a non-ionic disintegrating  
agent.

20

21. A tablet as claimed in claim 20 wherein the  
disintegrating agent is crospovidone present at  
about 0.5% to about 7% w/w.

25 22. A tablet comprising about 65% to about 85% w/w  
anhydrous crystalline valaciclovir hydrochloride  
including the d spacing diffraction pattern of  
claim 16, about 0.5% to about 5% w/w of povidone,  
about 3% to about 30% w/w of a cellulosic filler,  
about 0.5 to about 7% w/w of a non-ionic  
disintegrating agent, about 0.1% to about 1.0% of  
30 a stearate lubricant and about 0.1% to about 0.5%  
w/w of colloidal silicon dioxide, wherein the  
valaciclovir hydrochloride is present  
intraganularly; and wherein the cellulosic  
filler, stearate lubricant and colloidal silicon

35

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dioxide are present extragranularly.

23. A tablet as claimed in any one of claims 1 to 22 which is film coated.

5

24. A tablet as claimed in any one of the preceding claims for use in medical therapy.

25. A method of treatment of a herpes virus infection  
10 in a human comprising administering to the host one or more tablets as claimed in any one of the preceding claims to administer an effective anti-herpes viral amount of valaciclovir or a salt thereof.

15

26. A process for preparing a tablet comprising at least about 50% w/w valaciclovir or a salt thereof, a binding agent, a lubricant, and about 0.05 to about 3.0% colloidal silicon dioxide, wherein the friability of the tablet does not exceed 1% the hardness is at least 9 kP and the ejection force does not exceed 1000N; said process having the valaciclovir or its salt present within the granules of the tablet, and the lubricant and colloidal silicon dioxide present extragranularly.  
20

25

27. A process for preparing a tablet comprising at least about 50% w/w valaciclovir or a salt thereof, a binding agent, a filler, a lubricant, and about 0.05 to 3.0% w/w colloidal silicon dioxide; wherein the hardness of the tablet is at least 9 kp, the friability is not more than 1%, and the ejection force is not more than 1000N; said process comprising forming granules which include valaciclovir or a salt thereof and then blending the lubricant and colloidal silicon dioxide with  
30  
35

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said granules.

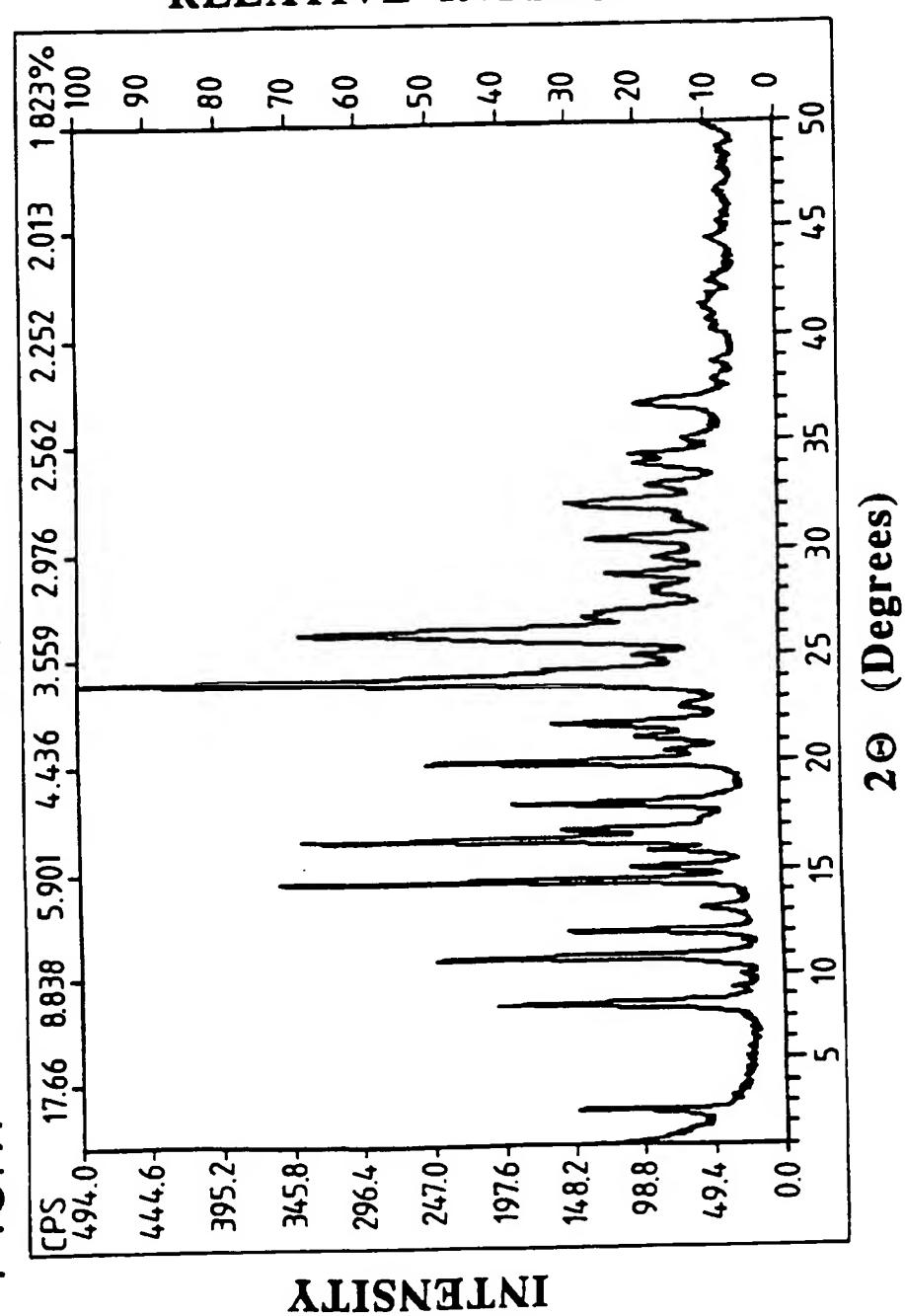
28. A according to claim 26 or 27 comprising forming granules by mixing said valaciclovir or salt, 5 optionally a binding agent or a portion thereof, and optionally the filler or a portion thereof; granulating with a granulating solution to form granules or dissolving the binding agent or a portion in the granulating solution before adding 10 to valaciclovir; drying the granules; blending the granules with the lubricant, colloidal silicon dioxide, and optional filler or a portion thereof; and then compressing the blended mixture to form a tablet.

15

29. A process for preparing a tablet comprising at least about 50% w/w valaciclovir or a salt thereof, a binding agent, a lubricant, about 0.05 to about 3% w/w colloidal silicon dioxide, and about 3 to 20 about 30% w/w of a cellulostic filler; wherein the hardness of the tablet is at least 9kP, the friability is not more than 1%, and the ejection force is not more than 1000N; said process comprising forming granules by mixing the valaciclovir or salt, optional binding agent or a portion thereof, and optionally a portion of cellulostic filler; granulating with a granulating solution to form granules or dissolving the binding agent or a portion thereof in the granulating 25 solution before adding to valaciclovir; drying the granules; blending the granules with the lubricant, colloidal silicon dioxide, and at least a portion of the cellulostic filler; and then compressing the 30 blended mixture to form a tablet.

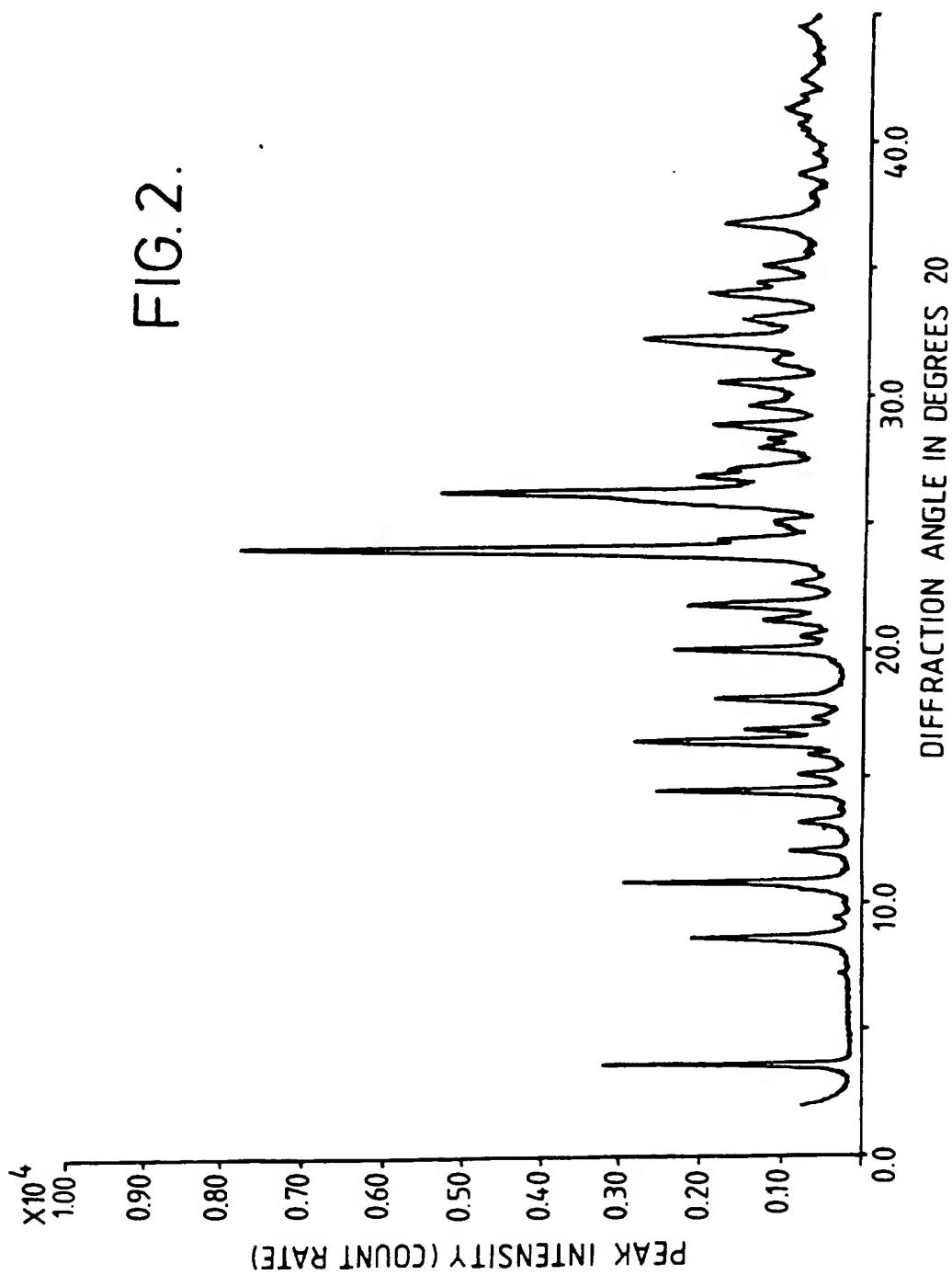
1/3

FIG. 1.



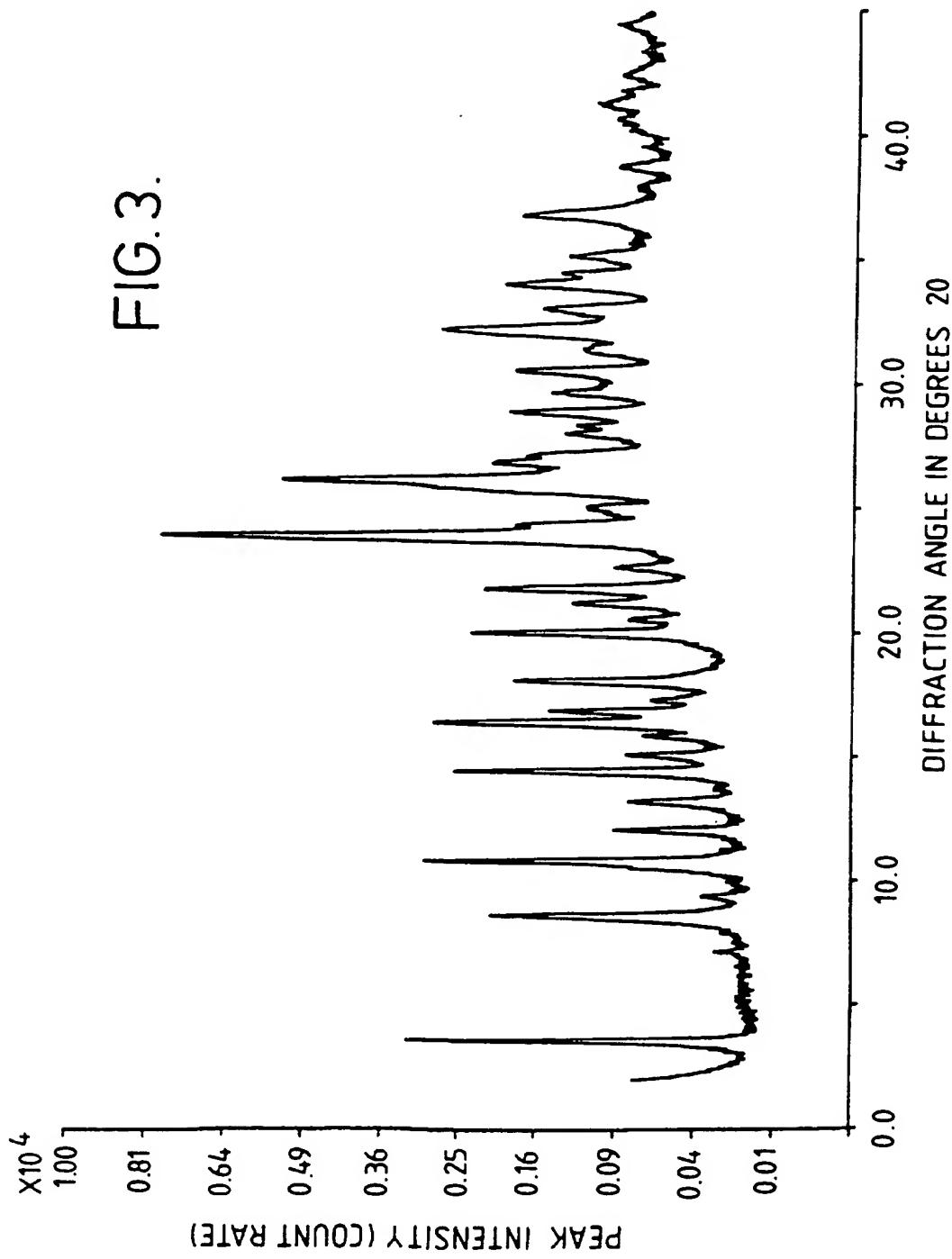
2/3

FIG. 2.



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FIG. 3.



**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/GB 96/00111

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/20 A61K47/02

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CHEMICAL ABSTRACTS, vol. 118, no. 10, 8 March 1993 Columbus, Ohio, US; abstract no. 87553, XPO02003233 see abstract &amp; ZHONGGUO YIYAO GONGYE ZAZHI, vol. 23, no. 8, 1992, page 350-1 YUAN, SONGFAN: "Preparation of ibuprofen" ---</p>	1-29
Y	<p>EP,A,0 308 065 (WELLCOME FOUND LTD) 22 March 1989 cited in the application see page 5, line 42 - page 6, line 3 see page 10, line 1 - page 11, line 20 ---</p>	1-29 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents:

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Date of the actual completion of the international search  17 May 1996	Date of mailing of the international search report  29.05.96
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Fax. 31 651 epo nl. Fax (+ 31-70) 340-3016	Authorized officer  Economou, D

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/00111

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CHEMICAL ABSTRACTS, vol. 69, no. 4,      22 July 1968      Columbus, Ohio, US;      abstract no. 11048,      XP002003234      see abstract      &amp; SB. TR., VSES.NAUCH.-ISSLED. INST. NOV.      STROIT. MATER.,      vol. 15, 1967,      page 15-21      EDEL'MAN, L.I.: "Effect of the nature and      particle size of fillers and methods for      adding components on the hardness of      poly(vinyl chloride) compositions."</p> <p>---</p>	1-29
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